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(54) Title: USE OF AZITHROMYCIN FOR THE TREATMENT OF ADULT PERIODONTITIS AND TOPICAL COMPOSITIONS FOR THIS USE

(57) Abstract

This invention relates to methods for treatment of adult periodontitis in a human or other animal subject, comprising administering to the subject having such disease a safe and effective amount of azithromycin. This invention also relates to compositions for use in such treatment.

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Use of azithromycin for the treatment of adult periodontitis and topical compositions for this use

Technical Field

This invention involves a novel use of azithromycin for treating adult periodontitis.

Background Of The Invention

Periodontal disease comprises a group of inflammatory conditions of periodontal tissues with a common etiologic agent: bacteria in the form of dental plaque. Periodontal disease is the most frequent cause of tooth loss in adults. After 40 years of age, the majority of the population exhibits some sign of periodontitis. Periodontitis develops following plaque accumulation and will not develop in the absence of plaque. If plaque is present, the bacteria metabolize and produce acids and toxins which can irritate the gums and cause gingival inflammation, gingivitis. Although not all gingivitis sites in the presence of plaque develop loss of connective tissue attachment and/or alveolar bone resorption (a disease called periodontitis) all periodontitis is preceded by gingivitis. Although it is unknown what triggers the conversion from gingivitis to periodontitis, it could be bacterial accumulation due to poor oral hygiene, or systemic factors, or a combination of these.

Tissue destruction may occur as a slow continuous process, or as the result of repeated episodes of active disease alternating with intervals of disease remission and repair. An individual may have sites within his or her mouth which are healthy and others which have varying stages of disease coexisting.

There are several different forms of periodontitis in humans. The distinct diseases may have different etiologies and are likely to progress and respond differently to a given therapy.

Common adult periodontitis is the most common form of periodontitis and typically does not appear until a subject is 35 years of age or older. It is preceded by gingivitis and the establishment of a pathogenic subgigival microflora. The presence of microbial deposits and calculus is usually commensurate with the amount of periodontal destruction. When host defenses are insufficient, specific pathogens in the subgingival microflora will increase and cause tissue breakdown. The subgingival microflora in periodontitis is very complex microbiota with elevated proportions of motile, gram-negative, capnophilic and anaerobic species. There are specific microorganisms that appear to be more strongly associated with these lesions.

The main microorganisms associated with adult periodontitis are: *Porphyromonas gingivalis, Prevotella intermedia; Eikenella corrodens, Fusobacterium nucleatum; Wolinella recta; Selenomonas sputigena; Eubacterium timidum, Eubacterium brachyii, Peptosteptococcus micros*; and spirochetes, including *Treponema denticola*.

Rapidly progressive periodontitis is a clinical condition which affects yound adults (20-35 years of age) with generalized sever and rapid bone loss. Overt clinical inflammation is not always seen. Small amounts of plaque and calculus may be present. The lesions are associated with elevated proportions of *Porphyromonas gingivalis, Bacteroides capillosus, Prevotella intermedia, Bacteroides forsythus, Actinobacillus* species, *Eikenella corrodens*, and *Wolinella recta* either individually or in different patterns.

Refractory adult periodontitis refers to periodontal lesions or clinical conditions which are refractory (unresponsive) to periodontal treatment. The microflora of these lesions are *Actinobacillus actinomycetemcomitans (A.a.), Porphyomonas gingivalis* and *Prevotella intermedia*. It has been theorized that this *group* of pathogens is reponsible for this clinical condition.

Juvenile periodontitis typically has an onset age around the age of puberty of a subject. The disease manifests itself as inflammation and rapid destruction of the peridontal tissues around more than one tooth in the permanent dentition. These lesions progress rapidly after onset but tend to slow with time. There is often (not always) a small amount of supragingival plaque and calculus which is not commensurate with the amount of destruction present. *A.a.* is the most frequently isolated species from subgingival microflora of sites experiencing disease. However, some subgingival pathogens isolated have also been found in elevated proportion in these lesions, including *Eikenella corrodens, Fusobacterium nucleatum, Bacteroides capillosus* and *Eubacterium brachyii*.

Prepubertal periodontits has its onset during or immediately following eruption of primary teeth (4-8 years of age). This disease typically manifests itself as a very severe and rapid peridontal destruction around the primary teeth. *A.a.* is the most prominent pathogen frequently associated with other microorganisms such as *Selenomonas sputigena, Prevotella intermedia*, and *Eikenella corrodens*.

Although some antibiotics are known to be useful in the treatment of adult periodontitis, not all are useful for such therapy. Some, such as tetracycline, tend to encourage the production of resistant strains of bacteria. Some antibiotics, those not having a long half-life, require multiple dosages per day to achieve efficacy. This is not very conducive to consistant

compliance by the patient. Some antibiotics can cause systemic complications, such as stomach upset and nausea.

Applicant has surprisingly discovered that compositions and methods of this invention using azithromycin are safe and effective for the treatment of adult periodontitis. Methods of this invention afford efficacy greater than methods among those described in the art. Azithromycin can be delivered perorally, systemically, or topically in the oral cavity.

Summary Of The Invention

This invention relates to methods for treatment of adult periodontitis in a human or other animal subject, comprising administering to the subject having such disease a safe and effective amount of azithromycin.

This invention also relates to compositions for use in such treatment.

Detailed Description Of The Invention

"Periodontal pocket" as used herein, means an abnormally deep gingival sulcus, which is due to the apical migration of the gingival attachment, associated with periodontitis.

"Periodontal disease" as used herein, means, those diseases which attack the gingiva and the underlying alveolar bone supporting the teeth. Periodontal disease includes gingivitis (inflammation of the gums), and all forms of periodontitis, as well as series of oral diseases exhibiting various syndromes which vary from each other according to the stage or situation of the disease or the age of the patient, and have not been definitely subclassified.

"Adult periodontitis" as used herein, refers to the forms of periodontitis typically associated with *Porphyromonas gingivalis* bacterium, and whose age of onset is about 20 years of age or older; such diseases can include common adult periodontitis, refractory adult periodontitis, and rapidly progressive periodontitis. Adult periodontitis is a condition whose predominant putative ediologic agent is not *Actinobacillus actinomycetemcomitans* ("*A.a.*"). "*A.a.*-associated periodontitis" refers to the clinical conditions of periodontitis whose predominant putative ediologic agent is the bacterium, *A.a.*; such clinical conditions can include juvenile periodontitis and prepubertal periodontitis.

This invention involves methods for treatment of adult periodontitis in a human or other animal subject, comprising administering to the subject having such disease a safe and effective amount of azithromycin. As used herein "safe and effective amount" means an amount of compound or composition sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and

effective amount of the compound or composition will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific compound or composition employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending health care provider.

Azithromycin, (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-a-*L*-*ribo*-hexopyranosyl)oxy]-2ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-b-*D*-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one is disclosed in the MERCK INDEX, 11th ed. (1989), S. Budavari, ed., No. 928, p. 146. Azithromycin is also described in U.S. Pat. No. 4,517,359, the disclosure of which is incorporated herein by reference. Also suitable for use in this invention are pharmaceutically-acceptable salts of azithromycin, including but not limited to the hydrochloride, tartrate, malate, malic, acetate, and sulfate salts.

Treatments of adult periodontitis utilizing azithromycin therapy may be achieved by delivering azithromycin systemically, e.g. through peroral dosage, or achieved through sustained release drug delivery, or achieved topically.

Compositions

Dose forms suitable for use in this invention include those which provide systemic delivery of azithromycin. Systemic dosage forms may be any form suitable and safe for human systemic administration, such as tablets, capsules, suspensions, injectable solutions, and other typical systemic dose forms well known in the field.

Peroral dosage compositions useful in the methods of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of drug, *i.e.* azithromycin or a pharmaceutically-acceptable salt thereof, that is suitable for administration to a human or other animal subject, in a single dose, according to good medical practice. These compositions preferably contain from about 10 mg (milligrams) to about 1,000 mg, more preferably from about 100 mg to about 750 mg, more preferably from about 250 mg to about 500 mg, also more preferably, from about 300 to about 400 mg of azithromycin or a pharmaceutically-acceptable salt thereof.

A variety of pharmaceutically-acceptable gastric delivery carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. The amount of carrier employed in conjunction with the azithromycin is sufficient to

provide a practical quantity of material for administration per unit dose. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references, each incorporated by reference herein: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2d Edition (1976).

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules, and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of azithromycin or a pharmaceutically-acceptable salt thereof. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents. Capsules are presently available under the trade name Zithromax™ and provided by Pfizer Inc.

Other dose forms useful in this invention include "sustained release oral drug delivery systems" which can provide sustained release of a drug topically in or around a periodontal lesion such as a periodontal pocket. Preferred compositions of this invention for use in treatment of adult periodontitis in a human or other animal subject comprise comprise: a) a safe and effective amount of azithromycin or a pharmaceutically-acceptable salt thereof; and b) a sustained release oral drug delivery system. Such sustained release oral drug delivery systems may utilize non-bioerodible, biocompatible polymers capable of being formed into a solid, such as those described in U.S. Pat. No. 5,114,718, issued May 19, 1992 to Damani, incorporated herein by reference. Such polymers may include polyurethanes, collagen, polyacrylates, elastomeric copolymers (including polyisobutylene and ethylene vinyl acetate copolymers), cellulosic polymers (including hydroxymethyl cellulose, hyroxyethyl cellulose, hydroxypropyl cellulose, hydroxybutyl cellulose and esters such as cellulose acetate and cellulose acetate phthalate), ethylene vinyl alcohol copolymers, polystyrene, polyvinyl chloride, polycarbonate, and polyethylene among many others. Preferred polymers are ethylene vinyl

acetate, polyisobutylene and polyurethane with ethylene vinyl acetate being the preferred material.

Sustained release oral drug delivery systems may also utilize bioerodible polymers such as those described in U.S. Pat. 5,198,220, issued Mar. 20, 1993 to Damani, and in U.S. Pat. No. 5,173, 299, issued Dec. 22, 1992 to Damani, both incorporated herein by reference. Other bioerodible polymers useful in this invention include those polymer materials which are safe for use in the oral cavity of a human or other animal, which are solubilized or plasticized by inclusion of leachable solvents and thereby hardened upon placement of compositions containing the polymer into the periodontal tissue, and which slowly degrade in the periodontal tissue. Such polymers are known, including for example polymers and copolymers such as glycerides, polyacrylates, polylactic acid ("PLA"), polyglycolic acid ("PLG"), polylactyl-co-glycolic acid ("PLGA"), polyaminoacids such as polyaspartate, chitosan, collagen, polyalbumin, gelatin, hydrolyzed animal protein, alginic acid and its derivatives, xanthan and other water soluble gums, polyanhydride, and poly orthoesters. Preferred are polymers and copolymers of polylactic acid ("PLA"), polyglycolic acid ("PLG"), and polylactyl-co-glycolic acid ("PLGA").

Preferred bioerodible polymers useful for this invention are the copolymers containing mixtures of lactide and glycolide monomers. Lactide monomeric species preferably comprise from about 15% to about 85%, most preferably from about 35% to about 65% of the polymers, while glycolide monomeric species comprise from about 15% to about 85% of the polymer, preferably from about 35% to about 65% on a molar basis. The molecular weight of the copolymer typically lies in the range of from about 1000 to about 120,000 (number average). These polymers are described in detail in U.S. Patent 4,443,430, April 17, 1984, to Mattei incorporated herein by reference.

The feature of fluid gel or paste-like compositions containing such copolymers is their transformation into near solid phase in the presence of aqueous fluid such as water, aqueous buffers, serum, crevicular fluid, or other body fluid. For example, when a sample of such a gel is placed into a tube containing water or human serum, the composition becomes nearly solid in the receptor phase. Thus, even though such fluid compositions can be used advantageously when desired from a syringe-like apparatus, they still offer the uncompromised advantages of solid devices at the treatment sites. Further, since such polymeric materials do undergo slow degradation, the drug continues to release in a sustained manner from such compositions and the composition does not need to be surgically removed following tissue regeneration.

Conventional methods and apparatuses may be used to formulate compositions of this invention. Combinations of polymers may be used. The polymers generally comprise from about 1% to about 90%, preferably from about 10% to about 70%, of the compositions/devices useful for the methods of this inventions. Generally, for the most preferred copolymers containing lactide and glycolide, less polymer is necessary as the amount of lactide is increased.

The amount of azithromycin used in sustained release oral drug delivery compositions of this invention may be from about 0.5% to about 95% preferably from about 5% to about 50%, more preferably from about 10% to about 35% by weight of the composition. The compositions/devices may be designed to release azithromycin to provide a minimum concentration of active drug of from about 1µg per milliliter crevicular fluid up to about 5000 µg per milliliter, more preferably from about 5 µg per milliliter to about 100 µg per milliliter crevicular fluid. One µg per milliliter crevicular fluid is substantially equivalent to 1 µg per gram gingiva.

Other dose forms suitable for use in this invention include traditional oral care compositions comprising a "pharmaceutically-acceptable topical oral carrier", as used herein, denotes a carrier for the active compound of this invention comprising solid or liquid filler diluents suitable for use in contact with the oral tissues of humans and lower animals without undue toxicity, incompatibility, instability, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio. Such topical oral carrier, when combined with an active of this invention, results in a composition which is administered topically to the oral cavity. Preferably such compositions are held in the oral cavity for a period of time, and then largely expectorated rather than being swallowed. Such compositions include dentifrice, toothpaste, mouthwash, mouth rinse, and dental rinse, chewing gum, and lozenge carriers.

Preferred topical oral compositions of this invention for use in treatment of adult periodontitis in a human or other animal subject comprise: a) a safe and effective amount of azithromycin or a pharmaceutically-acceptable salt thereof; and b) a pharmaceutically-acceptable topical oral carrier. Components of such compositions and topical oral carriers are described in U.S. Patent No. 4,994,262 issued Feb. 19, 1991, to Charbonneau et al., and in U.S. Pat. No. 4,990,329, issued Feb. 5, 1991, to Sampathkumar; both incorporated herein by reference.

If incorporated into a topical oral carrier, the azithromycin would be present at from about 0.01% to about 2% more preferably from about 0.1% to about 1%, more preferably still from about 0.1% to about 0.5% of a liquid

carrier, such as a mouthwash, or a dental rinse. If incorporated into a dentifrice topical oral carrier, the azithromycin would be present at from about 0.1% to about 20%, more preferably from about 1% to about 10%, more preferably still from about 15% to about 5%.

Methods of Use

This invention also relates to methods for treatment of adult periodontitis in a human or other animal subject, comprising administering to the subject having such disease a safe and effective amount of azithromycin.

Systemic dosage forms may be any form suitable and safe for human systemic administration, such as tablets, capsules, suspensions, injectable solutions, and other typical systemic dose forms well known in the field. Capsules are presently available under the trade name Zithromax™ and provided by Pfizer Inc.

Typically, the peroral dosage amounts of azithromycin may be from about 10 mg to about 1000 mg per dose, preferably from about 100 mg to about 750 mg, also more preferably still from about 250 mg to about 500 mg, also more preferably from about 300 mg to about 400 mg azithromycin. A dose is taken preferably from once every other day to about four times per day, more preferably from about once per day to about twice per day, more preferably once per day. More preferred still is a 500 mg dose once on a first day and a 250 mg dose once per day thereafter for from about 5 days to about 30 days, more preferably from about 5 days to about 10 days. Preferably no more than about 1000 mg azithromycin is ingested in any given day; more preferably, no more than about 500 mg is ingested in one day.

Sustained release compositions are administered by gently placing the product in subgingival cavities of infected teeth. If the composition is one which hardens when inserted into the gingival pocket, the composition may be administered with a syringe or like apparatus fitted with a needle or catheter. The composition is injected into or near the base of the pocket; the syringe tip is slowly withdrawn as the pocket is filled. If the composition is one which is solid when inserted, the composition may be inserted into the pocket using dental instruments, including but not limited to, cotton pliers, forceps, a refraction cord, and plastic instruments. A solid composition may be trimmed with a scalpel or other sharp instrument to fit a subgingival cavity before insertion. Depending on the size of the periodontal pocket into which sustained release drug delivery system is being inserted, from about 0.05 mL to about 2 mL, preferably from about 0.1 mL to about 1 mL of composition is used. If the composition is non-bioerodible, it should be removed from about

seven to about fourteen days after insertion. If the composition is bioerodible there should be no need to remove the composition after insertion.

If a topical oral carrier is used to deliver azithromycin, the compositions may be utilized in conventional fashion, preferably from about once weekly to about three times daily, more preferably from about twice weekly to about twice daily, more preferably still from about once daily to about twice daily.

EXAMPLES

The following non-limiting examples further describe and demonstrate preferred embodiments within the scope of the invention. The examples are given solely for illustration and are not to be construed as limitations of this invention, as many variations are possible without departing from the spirit and scope of the invention.

The compositions of this invention can be made using methods which are commonly used to produce oral care products.

Example I

The following is a representative example of a a syringeable gel composition.

Component	% wt of composition
Azithromycin	25
gliycerol monooletate	70
Hydroxypropyl methylcellulose	5

Glycerol monooleate is heated to about 60°C. Hydroxypropyl methylcellulose is dispersed with agitation to uniformity. Azythromycin is mixed at about 40°C to uniformity and the mixture is cooled to room temperature.

0.1 mL of the gel is applied by injecting the gel into the base of a gingival pocket with a syringe fitted with a needle. The syringe tip is withdrawn as the pocket is filled. Once inserted, the composition undergoes a phase transition to cubic crystalline phase with increased viscosity. The sustained release drug delivery system is removed after ten days. The result is reduced gingival inflammation and a decrease in pocket depth.

Example II

The following is a representative example of a sustained release composition for insertion into a peridontal pocket.

Component	% wt of composition
Polylactic-glycolic acid	64
Azythromycin	30
Propylene carbonate	6

The polylactic acid polymer having an average molecular weight of about 4000 is blended with azythromycin. Propylene carbonate, a plasticizer,

is added. The mixture is blended to uniformity at about 60°C. The blend is extruded to form desired shapes for their insertion into subgingival cavities.

A dentist inserts 0.05 mL of the extruded composition into a subgingival cavity of a subject having adult periodontitis using cotton pliers. The composition undergoes gradual degredation and does not need to be removed. The result is a reduction in gingival inflammation and pocketing.

Example III

The following is a representative example of a method of using peroral dosage forms of azithromycin.

A human subject afflicted with adult periodontitis ingests a dose of 500 mg of azithromycin in the form of two Zithromax™ capsules (250 mg of azithromycin each) on a first day. For each of five days immediately succeeding the first day, the subject ingests a dose of 250 mg azithromycin in the form of one Zithromax™ capsule per day. The result is a reduction in gingival inflammation and pocketing.

Example IV

The following is a representative example of a mouth rinse composition of this invention.

Component	Wt %
Azythromycin	0.1
EtOH (200 proof)	16.25
Surfactant (TWEEN 80)	0.12
Glycerin	10.
Saccharin	0.06
Flavor	0.041
F&DC Blue #1 (1% soln)	0.022
F&DC Yellow #5 (1% soln)	0.018
Benzoic acid	0.0045
Sodium Benzoate	0.054
Water	q.s.

A person introduces fifteen mL of the mouth rinse comprising azithromycin to the oral cavity. The liquid is then agitated for 90 seconds within the oral cavity to obtain a good distribution of the mouth rinse over the tissues of the oral cavity. Following agitation, the mouth rinse is expectorated from the oral cavity. This proceedure is done twice per day for total of ten days. The result is reduced gingival inflammation and pocket depth.

While particular embodiments of this invention have been described, it will be obvious to those skilled in the art that various changes and modifications to this invention can be made without departing from the spirit

and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

WHAT IS CLAIMED IS:

1. An oral composition for use in treatment of adult periodontitis in a human or other animal subject comprising:
   a) a safe and effective amount of azithromycin or a pharmaceutically-acceptable salt thereof; and
   b) a sustained release oral drug delivery system.

2. The composition of Claim 1, wherein the sustained release drug delivery system is a bioerodible polymer.

3. The composition of Claim 1, wherein the sustained release drug delviery system is a non-bioerodible polymer.

4. An oral composition for use in treatment of adult periodontitis in a human or other animal subject comprising:
   a) a safe and effective amount of azithromycin or a pharmaceutically-acceptable salt thereof; and
   b) a pharmaceutically-acceptable topical oral carrier.

5. The composition of Claim 4, wherein the topical oral carrier is selected from the group consisting of a dentifrice carrier, toothpaste carrier, a mouthwash carrier, a mouth rinse carrier, a lozenge carrier, and a chewing gum carrier.

6. A method for treatment of adult periodontitis in a human or other animal subject, comprising administering to the subject having such disease a safe and effective amount, preferably from 10 mg to 1000 mg per dose, of azithromycin or a pharmaceutically-acceptable salt thereof.

7. The method of Claim 6, wherein the azithromycin is in peroral dosage form.

8. The method of either of Claims 6 or 7, wherein the amount of azithromycin administered is from 250 mg to 500 mg per dose.

9. The method of any of Claims 6-8, wherein the arithromycin is incorporated into a sustained release drug delivery system.

10. The method of any of Claims 6-9, wherein the azithromycin is incorporated into a topical oral carrier.

INTERNATIONAL SEARCH REPORT

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PCT/US 94/10804

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP,A,0 430 474 (THE PROCTER & GAMBLE COMPANY) 5 June 1991 see page 3, line 34-38; claims & US,A,5 198 220 (IBID.) cited in the application	1,2
X,Y	EP,A,0 429 225 (THE PROCTER & GAMBLE COMPANY) 29 May 1991 see page 3, line 33-37; claims & US,A,5 173 299 (IBID.) cited in the application	1,2
X,Y	US,A,5 230 895 (R.F. CZARNECKI) 27 July 1993 see column 4, line 56-63; claims 1,14	1,2

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 December 1994	20. 12. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Orviz Diaz, P

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INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 94/10804

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